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A Synthesis of Substituted 2-Pyrones by Carbonylative Cross-Coupling-Thermolysis of 4-Halocyclobutenones With Alkenyl-, Aryl-, and Heteroarylstannanes

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Abstract

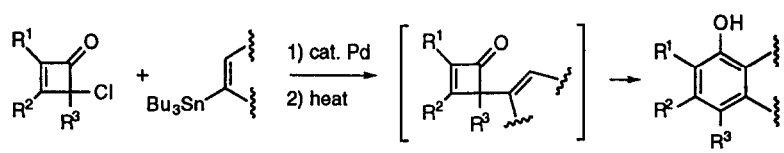
Palladium catalyzed carbonylative cross-coupling of 4-chloro-2,3-disubstituted-2-cyclobutenones with alkenyl-, aryl-, and heteroaryltin reagents and thermolysis provides a general method for the synthesis of 2,3,6-trisubstituted-2-pyrones. The reaction is regiospecific, coupling occurring preferentially at the 4-position of the cyclobutenone.

INTRODUCTION

2-Pyrones are valuable materials both as precursors to other compounds[1-5] or themselves as biologically interesting compounds.[6-10] Various synthetic approaches to pyrones have been described.[11-18]

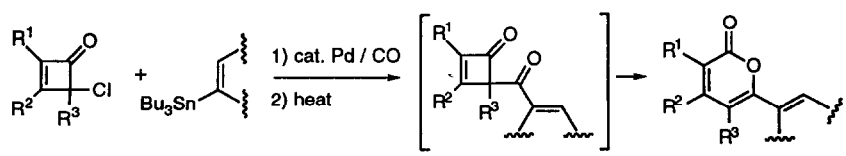
The palladium catalyzed cross-coupling of 4-chloro-2-cyclobutenones (1) with alkenyl, aryl, and heteroarylstannanes generates 4-R^{unsat}-2-cyclobutenones (2) that, on thermolysis, are converted into substituted phenols in a very general fashion (**Eqn. 1**).[19] By performing the carbon-carbon bond formation in the presence of CO, a carbonylative variant[20-22] of the cross-coupling should deliver transient 4-acyl-2-cyclobutenones (**3**)[12] that would rapidly convert to the isomeric pyrones (**Eqn. 2**). Described within is the successful implementation of this strategy leading to a novel protocol for the construction of substituted 2-pyrones.

Eqn. 1



1 **2**

Eqn. 2

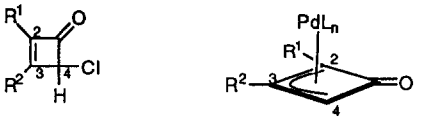


1 **3**

RESULTS AND DISCUSSION

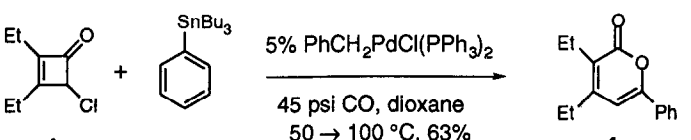
The palladium catalyzed carbonylative coupling of allyl halides and organotin reagents has been extensively investigated by Stille and coworkers.[23,24] The reaction can be carried out under mild conditions,

functional groups can be maintained in either coupling partner, double bond geometry in the substituted vinyltin reagent is retained, and the carbonylative coupling takes place exclusively at the least hindered site of allyl halide. To test the applicability of this chemistry to pyrone synthesis as suggested in **Equation 2**, a variety of 2,3-disubstituted-4-chloro-2-cyclobutenones were prepared following previously documented procedures.[19,25,26] Preferential coupling at the 4-position of the cyclobutenone was anticipated,[19,21] it becoming the less substituted terminus of the putative 4-oxocyclobutenylpalladium intermediate.



The feasibility of the projected carbonylative coupling reaction was tested with 4-chloro-2,3-diethyl-2-cyclobutenone (**1a**) and phenyltri-*n*-butylstannane. In the presence of various palladium catalysts under 15 psi of CO, little or no reaction occurred. However, under 45 psi of CO in dioxane at 50 °C for 8h then at 100 °C for an additional 8h, a 45% yield of the pyrone **4a** was generated using 5 mol% $Cl_2Pd(PPh_3)_2$ (**Eqn. 3**). Lower yields of product were observed when the reaction temperature was maintained at 50 °C. A similar yield of **4a** was also obtained by employing either $Cl_2Pd(PhCN)_2/AsPh_3$[27,28] or $Cl_2Pd(PhCN)_2$/tris-(2-furyl)phosphine[29] as catalyst. After some experimentation, the yield of **4a** was improved to 63% using 5% $PhCH_2PdCl(PPh_3)_2$ as catalyst (**Eqn. 3**).

Eqn. 3

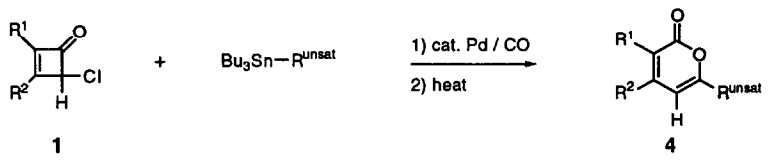


1a **4a**

Phenyltri-*n*-butylstannane also participated in carbonylative cross-coupling with other 4-chloro-2-cyclobutenones. As shown in entries 1 – 4 of the **Table**, 3,4-disubstituted-6-phenyl-2-pyrones **4a** – **4d** were obtained in good yields under mild reaction conditions. Moreover, the carbonylative cross-coupling took place exclusively at the least hindered allylic terminus in every case. This reaction was successfully extended to other arylstannanes (*p*-chlorophenyltri-*n*-butylstannane and *p*-methoxyphenyltri-*n*-butylstannane)[30,31] and heteroarylstannanes (N-methyl-2-tri-*n*-butylstannylpyrrole,[32] 2-tri-*n*-butylstannylfuran,[33] 3-tri-*n*-butylstannylfuran,[34] and 2-tri-*n*-butylstannylthiophene[35]). High yields of products were obtained in all cases.

Similar results were obtained when alkenyltri-*n*-butyltin reagents were employed. 2,3-Diethyl-6-ethenyl-2-pyrone was obtained by treating 4-chloro-2,3-diethyl-2-cyclobutenone and vinyltri-*n*-butyltin with 5 mol% $PhCH_2PdCl(PPh_3)_2$ under 45 psi of CO. The use of 1-ethoxyvinyltri-*n*-butyltin and 1-propenyltri-*n*-butylstannane[36] as reaction partners was also examined. It was observed that the 6-alkenyl substituted 2-pyrone products were noticeably less stable than their 6-aryl and 6-heteroaryl counterparts, and decomposed upon standing.

Table. Pyrone Synthesis by Carbonylative Cross-Coupling of 4-Chlorocyclobutenones and Organostannanes.



1 4

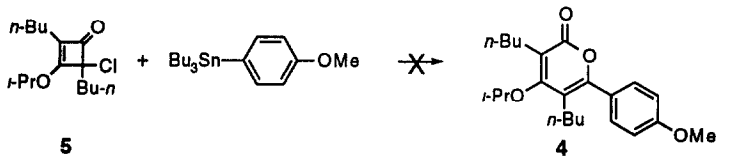
Entry	Cmpd	R^1	R^2	R^{unsat}	Product	Yield (%)
1	**1a**	Et	Et	Ph	**4a**	63
2	**1b**	*n*-Bu	*n*-Bu	Ph	**4b**	86
3	**1c**	Me	Ph	Ph	**4c**	78
4	**1d**	Me	*i*-PrO	Ph	**4d**	60
5	**1a**	Et	Et	*p*-ClC_6H_4	**4e**	84
6	**1b**	*n*-Bu	*n*-Bu	*p*-ClC_6H_4	**4f**	67
7	**1a**	Et	Et	*p*-$(MeO)C_6H_4$	**4g**	80
8	**1b**	*n*-Bu	*n*-Bu	*p*-$(MeO)C_6H_4$	**4h**	60
9	**1c**	Me	Ph	*p*-$(MeO)C_6H_4$	**4i**	76
10	**1d**	Me	*i*-PrO	*p*-$(MeO)C_6H_4$	**4j**	62
11	**1d**	Me	*i*-PrO	2-furyl	**4k**	89
12	**1a**	Et	Et	3-furyl	**4l**	80
13	**1b**	*n*-Bu	*n*Bu	3-furyl	**4m**	68
14	**1b**	*n*-Bu	*n*-Bu	2-thienyl	**4n**	72
15	**1d**	Me	*i*-PrO	2-thienyl	**4o**	74
16	**1b**	*n*-Bu	*n*-Bu	N-methyl-2-pyrrolyl	**4p**	60
17	**1a**	Et	Et	vinyl	**4q**	62
18	**1b**	*n*-Bu	*n*-Bu	2-ethoxyvinyl	**4r**	60
19	**1a**	Et	Et	1-propenyl	**4s**	65

As illustrated above, 2,3-disubstituted-4-chloro-2-cyclobutenones participated in carbonylative coupling with organotin reagents with high regioselectivity giving 3,4,6-trisubstituted-2-pyrones in good yields. Assignment of substitution pattern to the 2-pyrone products rests with spectroscopic arguments previously advanced[13] and to the identity of 2,3-diethyl-6-phenyl-2-pyrone and 2,3-diethyl-6-ethenyl-2-pyrone with previously described compounds.[13]

Although many alkenyl-, aryl- and heteroaryltin reagents readily underwent carbonylative cross-coupling with 2,3-disubstituted-4-chlorocyclobutenones to form the desired substituted 2-pyrones in good yields, neither 2-tri-*n*-butylstannyl-, nor 3-tri-*n*-butylstannylpyridine[37,38] nor the fully saturated tetra-*n*-butylstannane gave 2-pyrone products on palladium catalyzed reaction with 4-chloro-2,3-diethyl-2-cyclobutenone under a CO atmosphere. Furthermore, a fully substituted 4-chloro-2-cyclobutenone, 4-chloro-2,4-di-*n*-butyl-3-(1-methylethoxy)-2-cyclobutenone,[25] **5**, was prepared and subjected to reaction with *p*-methoxyphenyltri-*n*-

butyltin in the presence of 5 mol% $PhCH_2PdCl(PPh_3)_2$ under 45 psi of CO as shown in **Equation 4**. Unfortunately, no pyrone product was obtained.

Eqn. 4



5 4

CONCLUSIONS

In conclusion, palladium catalyzed carbonylative cross-coupling of 4-chloro-2,3-disubstituted-2-cyclobutenones with alkenyl-, aryl- and heteroaryltin reagents provided a general method for the synthesis of 2,3,6-trisubstituted-2-pyrones. The reaction is regiospecific and good yields of products are obtained.

EXPERIMENTAL SECTION

MATERIALS AND METHODS.

Thin layer chromatography (TLC) was effected using precoated 0.25 mm silica gel 60F-254 plates from EM Reagents and visualized by UV light, phosphomolybdic acid, vanillin, and anisaldehyde stain. Routine column chromatography was carried out using flash grade silica gel 60 (EM Science) with compressed air as the source of positive pressure unless stated otherwise. Solvents were dried prior to use. Tetrahydrofuran and Et_2O were distilled from sodium and benzophenone under nitrogen or argon. Methylene chloride, acetonitrile, triethylamine and TMSCl were distilled from calcium hydride. Dioxane was purchased from Aldrich in Sure-Sealed™ bottles. Air sensitive reactions were conducted under an atmosphere of argon or nitrogen in flame- or oven-dried glassware using standard airless techniques.

STARTING MATERIALS.

Palladium complexes were obtained from commercial sources and used as received: $PhCH_2PdCl(PPh_3)_2$ (Aldrich), $Cl_2Pd(PhCN)_2$ (Alfa) and $Cl_2Pd(PPh_3)_2$ (Johnson Matthey). Tris(2-furyl)phosphine was prepared according to a literature method.[39] Triphenylarsine was purchased from Aldrich. Phenyltri-*n*-butyltin and *p*-chlorophenyltri-*n*-butyltin were prepared according to the procedure reported by Azizan et al.[30] N-Methyl-2-tri-*n*-butylstannylpyrrole was prepared according to the procedure reported by Bailey.[32] 2-Tri-*n*-butylstannylthiophene was prepared according to the procedure reported by Gopinatham et al.[35] 1-Tri-*n*-butylstannyl propene was prepared according to the procedure reported by Seyferth and Vaughan.[36]

***p*-Methoxyphenyltri-*n*-butyltin.** *p*-Bromoanisole (5.124 g, 27.39 mmol, 1.0 equiv) was dissolved in 80 mL of dry THF and cooled to -78 °C. *n*-BuLi (14.70 mL, 2.5 M in hexanes, 34.24 mmol, 1.25 equiv) was added dropwise. The solution was stirred at -78 °C for 1 h and *n*-Bu_3SnCl (10.699 g, 32.87 mmol, 1.2 equiv) was added dropwise. The mixture was stirred for an additional 1 h at -78 °C, quenched with 10% aqueous NH_4Cl, and warmed to room temperature. Extraction with Et_2O (3 x 60 mL), drying of the combined organic layers ($MgSO_4$), filtration and removal of solvent left an oil that was purified by chromatography (flash SiO_2, 1 : 4 EtOAc / hexanes, $R_f = 0.42$) to give 9.248 g (85%) of product as a colorless oil: IR (CH_2Cl_2, cm^{-1}) 2960, 2929, 2873, 2856, 1586, 1547, 1495, 1465; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30 (d, J = 8.4 Hz, 2H), 6.90 (d, J = 8.4 Hz, 2H), 3.79 (s, 3H), 1.53 - 1.49 (m, 6H), 1.37-1.30 (m, 6H), 1.04 - 0.91 (m, 6H), 0.93 - 0.85 (m, 9H). All spectral data identical to that reported by Wardell et al.[31]

2-Tri-*n*-butylstannylfuran.[33] Furan (4.160 g, 61.10 mmol, 1.0 equiv) was dissolved in 120 mL of anhydrous Et_2O and cooled to -78 °C. TMEDA (10.14 mL, 67.22 mmol, 1.1 equiv) was introduced. After *n*-

BuLi (26.89 mL, 2.5 M in hexanes, 67.22 mmol, 1.1 equiv) was added, the solution was stirred under N_2 at -78 °C for 1 h. The reaction was allowed to warm to room temperature and stirred for 3 h and then cooled to -78 °C. Bu_3SnCl was added dropwise via syringe and stirred for 1 - 2 h at -78 °C. The reaction was quenched with 10% aqueous NH_4Cl and extracted with 3 x 70 mL Et_2O. The combined Et_2O layers were dried with Na_2SO_4 and concentrated to an oil. The resulting crude oil was purified by distillation to give 17.032 g (78%) of a clear yellow oil: bp 90 - 92 °C / 0.025 mmHg; IR ($CHCl_3$, cm^{-1}) 2960, 2929, 2873, 1466, 1140, 1075, 998; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, J = 1.2 Hz, 1H), 6.54 (d, J = 3.3 Hz, 1H), 6.40 (m, 1H), 1.63 - 1.49 (m, 6H), 1.40 - 1.22 (m, 6H), 1.12 - 1.00 (m, 6H), 0.91, 0.85 (t, J = 7.5 Hz, 9H).

3-Tri-*n* butylstannylfuran.[34] 3-Bromofuran (10 g, 68.04 mmol, 1.0 equiv) was dissolved in 150 mL of THF and cooled to -78 °C. 2.5 M *n*-BuLi in hexanes (24.94 mL, 74.84 mmol, 1.1 equiv) was added dropwise and stirred for 1 h. After *n*-Bu_3SnCl was added, the mixture was stirred for an additional 1 - 2 h at -78 °C. The reaction was quenched with 10 % aq NH_4Cl and extracted with 3 x 70 mL Et_2O, and the combined Et_2O layers were dried with Na_2SO_4, filtered and concentrated to an oil. The resulting crude oil was purified by distillation to give 18.222 g (75%) of a clear yellow oil: bp 110 - 112 °C / 0.025 mmHg; IR ($CHCl_3$, cm^{-1}) 2960, 2927, 1466, 1378, 1025, 909, 876; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56 (s, 1H), 7.23 (d, J = 3.9 Hz, 1H), 6.35 (d, J = 3.9 Hz, 1H), 1.57 - 1.00 (m, 18H), 0.89 (t, J = 7.2 Hz, 9H). All spectral data for 3-tri-*n*-butylstannylfuran were in accord with those reported by Fleming and Taddei.[34]

4-Chlorocyclobutenones were prepared according to literature procedures: 4-chloro-2,3-diethyl-2-cyclobutenone, **1a**,[25] 4-chloro-2,3-di-*n*-butyl-2-cyclobutenone, **1b**,[40] 4-chloro-2-methyl-3-phenyl-2-cyclobutenone, **1c**,[19] 4-chloro-2-methyl-3-(1-methylethoxy)-2-cyclobutenone, **1d**,[19] 4-chloro-2,4-di-*n*-butyl-3-(1-methylethoxy)-2-cyclobutenone, **5**.[25]

TYPICAL PROCEDURE FOR THE PALLADIUM CATALYZED CARBONYLATIVE CROSS-COUPLING OF 4-CHLOROCYCLOBUTENONES WITH ORGANOSTANNANES AND REARRANGEMENT TO 2-PYRONES.

3,4-Diethyl-6-phenyl-2-pyrone (4a).[13] A dioxane solution (12 mL) of 4-chloro-2,3-diethyl-2-cyclobutenone (0.286 g, 1.8 mmol, 1.0 equiv) was prepared in a Fischer-Porter pressure tube (3 oz. obtained from Lab-Crest Scientific Division) containing a magnetic stirring bar and equipped with a pressure gauge. The solution was degassed under nitrogen and treated with $PhCH_2PdCl(PPh_3)_2$ (68 mg, 5 mol%). The mixture was stirred for 10 min at room temperature until all solids had dissolved. The solution was then brought under 1 atm CO - (**CAUTION!**) at room temperature and a dioxane solution (2 mL) of phenyltri-*n*-butyltin (0.727 g, 1.98 mmol, 1.1 equiv) was cannulated into the reaction vessel with stirring for 10 min during which time the color changed from light yellow to orange. The Fischer-Porter tube was assembled and pressurized to 45 psi with CO. In a well-ventilated hood, the tube was placed in a deep oil bath maintained at 50 °C for 8 h. The progress of the reaction was monitored by CO uptake, a 5.0 mmol scale reaction typically reducing the CO pressure in the tube to 12 psi. The mixture was then heated to 100 °C for an additional 8 h to insure complete reaction. The reaction vessel was cooled to room temperature and CO was vented into the hood. The resulting black reaction mixture was partitioned between Et_2O (25 mL) and water (20 mL). The water layer was washed with Et_2O (2 x 25 mL) and the combined Et_2O layers were dried ($MgSO_4$) and concentrated to an oil. The resulting orange oil was purified by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.40) and dried *in vacuo* to give 0.259 g (63%) of **4a** as a yellow solid: mp 92 - 93 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1705, 1638; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.78 - 7.75 (m, 2H), 7.40 - 7.37 (m, 3H), 6.49 (s, 1H), 2.57 - 2.45 (m, 4H), 1.20 (t, J

= 7.5 Hz, 3H), 1.12 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.2, 156.5, 154.6, 131.5, 130.0, 128.6, 125.0, 124.7, 103.6, 25.7, 19.8, 13.5, 13.2. Analysis Calcd. for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 78.77; H, 7.08.

3,4-Di-*n*-butyl-6-phenyl-2-pyrone, 4b. A dioxane solution (12 mL) of 4-chloro-2,3-di-*n*-butyl-2-cyclobutenone (0.386 g, 1.8 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (68 mg, 5 mol%) was treated with phenyltri-*n*-butyltin (0.727 g, 1.98 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psi of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.43) gave 0.440 g (86%) of **4b** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1704, 1638; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.77 - 7.74 (m, 2H), 7.38 - 7.36 (m, 3H), 6.47 (s, 1H), 2.51 - 2.42 (m, 4H), 1.56 - 1.34 (m, 8H), 0.93 - 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.8, 155.7, 153.2, 131.0, 129.4, 128.1, 124.5, 123.3, 103.4, 31.9, 30.8, 30.4, 25.9, 22.3, 22.1, 13.3, 13.3; HRMS (EI) Calcd. for $C_{19}H_{24}O_2$: 284.1776. Found: 284.1774.

4,6-Diphenyl-3-methyl-2-pyrone, 4c. A dioxane solution (12 mL) of 4-chloro-2-methyl-3-phenyl-2-cyclobutenone (0.347 g, 1.8 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (68 mg, 5 mol%) was treated with phenyltri-*n*-butyltin (0.727 g, 1.98 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.56) gave 0.368 g (78%) of **4c** as a yellow solid: mp 108 - 109 °C (CH_2Cl_2/ hexanes); IR (CH_2Cl_2, cm^{-1}) 1710, 1636; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 - 7.79 (m, 2H), 7.50 - 7.40 (m, 6H), 7.36 - 7.33 (m, 2H), 6.65 (s, 1H), 2.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.5, 164.0, 156.4, 152.1, 137.9, 131.5, 130.3, 128.9, 128.0, 127.9, 125.3, 119.8, 104.5, 14.1. Analysis Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.37. Found: C, 82.46; H, 5.43.

3-Methyl-4-(1-methylethoxy)-6-phenyl-2-pyrone, 4d. A dioxane solution (14 mL) of 4-chloro-2-methyl-3-(1-methylethoxy)-2-cyclobutenone (0.347 g, 1.99 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (75 mg, 5 mol%) was treated with phenyltri-*n*-butyltin (0.803 g, 2.19 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.45) gave 0.292 g (60%) of **4d** as a yellow solid: mp 99 - 100 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1706, 1640; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.79 - 7.76 (m, 2H), 7.42 - 7.40 (m, 3H), 6.57 (s, 1H), 4.68 (heptet, J = 6.0 Hz, 1H), 1.93 (s, 3H), 1.37 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.63, 163.93, 157.76, 131.04, 129.95, 128.22, 124.88, 103.00, 93.32, 71.21, 21.87, 8.33.

Analysis Calcd. for $C_{15}H_{16}O_2$: C, 73.75; H, 6.60. Found: C, 73.71; H, 6.62.

6-(*p*-Chlorophenyl)-3,4-diethyl-2-pyrone, 4e. A dioxane solution (14 mL) of 4-chloro-2,3-diethyl-2-cyclobutenone (0.331 g, 2.09 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (79 mg, 5 mil %) was treated with *p*-chlorophenyltri-*n*-butyltin (0.922 g, 2.29 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psi of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.42) gave 0.462 g (84%) of **4e** as a pale yellow solid: mp 124 - 125 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1708, 1638; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.67 (d, J = 8.40 Hz, 2H), 7.32 (d, J = 8.40 Hz, 2H), 6.44 (s, 1H), 2.53 - 2.43 (m, 4H), 1.17 (t, J = 7.5 Hz, 3H), 1.08 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 154.8, 154.0, 135.4, 129.5, 128.3, 125.8, 124.6, 103.3, 25.2, 19.3, 13.0, 12.7. Analysis Calcd. for $C_{15}H_{15}O_2Cl$: C, 68.57; H, 5.75. Found: C, 68.65; H, 5.77.

6-(*p*-Chlorophenyl)-3,4-di-*n*-butyl-2-pyrone, 4f. A dioxane solution (12 mL) of 4-chloro-2,3-di-*n*-butyl-2-cyclobutenone (0.388 g, 1.81 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (68 mg, 5 mol%) was treated with *p*-

chlorophenyltri-*n*-butyltin (0.798 g, 1.99 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.45) gave 0.386 g (67%) of **4f** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1706, 1638; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.65 (d, *J* = 8.7 Hz, 2H), 7.32 (d, *J* = 8.7 Hz, 2H), 6.43 (s, 1H), 2.48 - 2.39 (m, 4H), 1.54 - 1.34 (m, 8H), 0.97 - 0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.4, 154.5, 153.0, 135.4, 129.5, 135.4, 129.5, 128.4, 125.8, 123.7, 103.6, 31.9, 30.7, 30.3, 25.9, 22.2, 22.1, 13.3, 13.2. Analysis Calcd. for $C_{19}H_{23}O_2Cl$: C, 71.40; H, 7.34. Found: C, 71.32; H, 7.37.

3,4-Diethyl-6-(*p*-methoxyphenyl)-2-pyrone, 4g. A dioxane solution (13 mL) of 4-chloro-2,3-diethyl-2-cyclobutenone (0.293 g, 1.85 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (67 mg, 5 mol%) was treated with *p*-methoxyphenyltri-*n*-butyltin (0.807 g, 2.03 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.30) gave 0.384 g (80%) of **4g** as a yellow solid: mp 86 - 87 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1702, 1634, 1607; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.73 (d, *J* = 8.40 Hz, 2H), 6.90 (d, *J* = 8.40 Hz, 2H), 6.39 (s, 1H), 3.81 (s, 3H), 2.53 - 2.46 (m, 4H), 1.20 (t, *J* = 7.50 Hz, 3H), 1.10 (t, *J* = 7.50 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.4, 161.1, 156.8, 155.0, 132.1, 126.7, 124.2, 123.5, 114.1, 113.4, 102.2, 55.3, 52.1, 19.8, 13.6, 13.3; Analysis Calcd. for $C_{16}H_{18}O_3$: C, 74.39; H, 7.02. Found: C, 74.42; H, 7.01.

3,4-Di-*n*-butyl-6-(p-methoxyphenyl)-2-pyrone, 4h. A dioxane solution (13 mL) of 4-chloro-2,3-di-*n*-butyl-2-cyclobutenone (0.402 g, 1.87 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (71 mg, 5 mol%) was treated with *p*-methoxyphenyltri-*n*-butyltin (0.819 g, 2.06 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.37) gave 0.354 g (60%) of **4h** as a pale yellow oil: IR (CH_2Cl_2, cm^{-1}) 1706, 1634, 1609; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, *J* = 9.0 Hz, 2H), 6.89 (d, *J* = 9.0 Hz, 2H), 6.36 (s, 1H), 3.80 (s, 3H), 2.50 - 2.40 (m, 4H), 1.53 - 1.36 (m, 8H), 0.96 - 0.88 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.5, 161.0, 156.4, 154.0, 126.7, 124.2, 122.6, 114.0, 102.6, 55.2, 32.4, 31.3, 31.0, 26.3, 22.8, 22.6, 13.9, 13.8. Analysis Calcd. for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.14; H, 8.32.

3-Methyl-6-(*p*-methoxyphenyl)-4-phenyl-2-pyrone, 4i. A dioxane solution (12 mL) of 4-chloro-2-methyl-3-phenyl-2-cyclobutenone (0.336 g, 1.75 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (66 mg, 5 mol%) was treated with *p*-methoxyphenyltri-*n*-butyltin (0.763 g, 1.93 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.35) gave 0.388 g (76%) of **4i** as a yellow solid: mp 154 - 155 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1706, 1634, 1609; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 (d, *J* = 8.40 Hz, 2H), 7.45 - 7.43 (m, 3H), 7.34 - 7.32 (m, 2H), 6.90 (d, *J* = 8.40 Hz, 2H), 6.51 (s, 1H), 3.81 (s, 3H), 2.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 165.1, 162.3, 157.5, 153.4, 139.0, 129.8, 129.6, 128.9, 127.9, 125.0, 119.4, 115.2, 104.1, 56.4, 15.0. Analysis Calcd. for $C_{19}H_{16}O_3$: C, 78.07; H, 5.52. Found: C, 78.00; H, 5.53.

6-(*p*-Methoxyphenyl)-3-methyl-4-(1-methylethoxy)-2-pyrone, 4j. A dioxane solution (12 mL) of 4-chloro-2-methyl-3-(1-methylethoxy)-2-cyclobutenone (0.320 g, 1.83 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (69 mg, 5 mol%) was treated with *p*-methoxyphenyltri-*n*-butyltin (0.801 g, 2.02 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C an for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.18) gave 0.276 g (62%) of **4j** as a yellow solid: mp 126 - 127 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1702, 1636, 1609; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, *J* = 8.70 Hz,

2H), 6.90 (d, J = 8.7 Hz, 2H), 6.44 (s, 1H), 4.66 (heptet, J = 6.0 Hz, 1H), 3.80 (s, 3H), 1.92 (s, 3H), 1.34 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.3, 165.8, 162.4, 159.4, 128.0, 125.1, 115.1, 103.3, 93.3, 72.6, 56.3, 23.4, 9.8. Analysis Calcd. for $C_{16}H_{18}O_4$: C, 70.06; H, 6.61. Found: C, 69.91; H, 6.51.

6-(2-Furyl)-3-methyl-4-(1-methylethoxy)-2-pyrone, 4k. A dioxane solution (13 mL) of 4-chloro-2-methyl-3-(1-methylethoxy)-2-cyclobutenone (0.324 g, 1.85 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (70 mg, 5 mol%) was treated with 2-tri-*n*-butylstannylfuran (0.728 g, 2.04 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.25) gave 0.387 g (89%) of **4k** as a yellow solid: mp 93 - 94 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1706, 1648; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37 (d, J = 1.0 Hz, 1H), 6.83 (d, J = 3.3 Hz, 1H), 6.42 (s, 1H), 6.39 (dd, J = 1.0 Hz, J = 3.3 Hz, 1H), 4.57 (heptet, J = 6.0 Hz, 1H), 1.83 (s, 3H), 1.27 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 164.3, 164.2, 150.2, 146.4, 144.2, 112.2, 111.1, 102.7, 92.0, 71.8, 22.3, 8.8. HRMS (EI) Calcd. for $C_{13}H_{14}O_4$: 234.0892. Found: 234.0892.

3,4-Diethyl-6-(3-furyl)-2-pyrone, 4l. A dioxane solution (12 mL) of 4-chloro-2,3-diethyl-2-cyclobutenone (0.286 g, 1.8 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (64 mg, 5 mol %) was treated with 3-tri-*n*-butylstannylfuran (0.709 g, 1.98 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and then at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc/ hexanes, R_f = 0.57) gave 0.319 g (80%) of **4l** as a yellow solid: mp 62 - 63 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1708, 1648; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (s, 1H), 7.38 (d, J = 1.2 Hz, 1H), 6.56 (s, 1H), 6.12 (s, 1H), 2.48 - 2.40 (m, 4H), 1.13 (t, J = 7.5 Hz, 3H), 1.05 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 154.2, 151.2, 143.5, 141.0, 123.6, 119.4, 106.3, 102.7, 25.0, 19.2, 12.9, 12.7. Analysis Calcd. for $C_{13}H_{14}O_3$: C, 71.54; H, 6.47. Found: C, 71.45; H, 6.46.

3,4-Di-*n*-butyl-6-(3-furyl)-2-pyrone, 4m. A dioxane solution (12 mL) of 4-chloro-2,3-di-*n*-butyl-2-cyclobutenone (0.378 g, 1.76 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (67 mg, 5 mol%) was treated with 3-tri-*n*-butylstannylfuran (0.691 g, 1.94 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 10 EtOAc / hexanes, R_f = 0.25) gave 0.3278 g (68%) of **4m** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1715, 1648; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (s, 1H), 7.37 (d, J = 1.5 Hz, 1H), 6.55 (s, 1H), 6.11 (d, J = 1.5 Hz, 1H), 2.43 - 2.33 (m, 4H), 1.49 - 1.29 (m, 8H), 0.90 - 0.84 (m, 6H). HRMS (EI) Calcd. for $C_{17}H_{22}O_3$: 274.1569. Found: 274.1575.

3,4-Di-*n*-butyl-6-(2-thienyl)-2-pyrone, 4n. A dioxane solution (13 mL) of 4-chloro-2,3-di-*n*-butyl-2-cyclobutenone (0.411 g, 1.91 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (72 mg, 5 mol%) was treated with 2-tri-*n*-butylstannylthiophene (0.786 g, 2.10 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.52) gave 0.398 g (72%) of **4n** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1708, 1632; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47 (d, J = 3.6 Hz, 1H), 7.30 (d, J = 5.1 Hz, 1H), 7.01 - 6.99 (m, 1H), 6.27 (s, 1H), 2.46 - 2.36 (m, 4H), 1.52 - 1.33 (m, 8H), 0.93 - 0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.0, 153.2, 151.6, 134.8, 127.4, 127.0, 125.6, 122.8, 102.6, 31.8, 30.7, 30.4, 25.9, 22.2, 22.1, 13.3, 13.2; HRMS (EI) Calcd. for $C_{17}H_{22}SO_2$: 290.1341. Found: 290.1354.

3-Methyl-4-(1-methylethoxy)-6-(2-thienyl)-2-pyrone, 4o. A dioxane solution (13 mL) of 4-chloro-2-methyl-3-(1-methylethoxy)-2-cyclobutenone (0.322 g, 1.85 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (70 mg, 5 mol%) was treated with tri-*n*-butylstannylthiophene (0.758 g, 2.03 mmol, 1.1 equiv) in 2 mL of dioxane at 45

psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.30) gave 0.342 g (74%) of **4o** as a yellow solid: mp 115 - 116 °C (CH_2Cl_2 / hexanes); IR (CH_2Cl_2, cm^{-1}) 1715, 1648; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, *J* = 3.6 Hz, 1H), 7.39 (d, *J* = 1.0 Hz, 1H), 7.06 (dd, *J* = 1.0 Hz, *J* = 3.6 Hz, 1H), 6.39 (s, 1H), 4.65 (heptet, *J* = 6.0 Hz, 1H), 1.93 (s, 3H), 1.37 (d, *J* = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.9, 163.8, 153.4, 134.7, 127.65, 127.60, 126.4, 102.4, 92.3, 71.3, 21.8, 8.4. Analysis Calcd. for $C_{13}H_{14}O_3S$: C, 62.38; H, 5.64. Found: C, 62.19; H, 5.58.

3,4-Di-*n*-butyl-6-(N-methyl-2-pyrrolyl)-2-pyrone, 4p. A dioxane solution (13 mL) of 4-chloro-2,3-di-*n*-butyl-2-cyclobutenone (0.402 g, 1.87 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (71 mg, 5 mol%) was treated with N-methyl-2-tri-*n*-butylstannylpyrrole (0.763 g, 2.06 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.38) gave 0.323 g (60%) of **4p** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1706, 1630; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.66 (s, br, 1H), 6.55 - 6.53 (m, 1H), 6.16 (s, 1H), 6.09 - 6.07 (m, 1H), 3.83 (s, 3H), 2.48 - 2.38 (m, 4H), 1.53 - 1.35 (m, 8H), 0.95 - 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 163.0, 154.4, 151.9, 127.3, 125.3, 121.2, 112.1, 108.2, 103.6, 36.8, 32.4, 31.3, 31.0, 26.3, 22.8, 22.6, 13.9, 13.8. HRMS (EI) Calcd. for $C_{18}H_{25}O_2N$: 287.1885. Found: 287.1883.

3,4-Diethyl-6-(1-vinyl)-2-pyrone, 4q.[13] A dioxane solution (12 mL) of 4-chloro-2,3-diethyl-2-cyclobutenone (0.286 g, 1.8 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (68 mg, 5 mol %) was treated with vinyltri-*n*-butyltin (0.629 g, 1.98 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and then at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.57) gave 0.199 g (62%) of **4q** as a pale yellow oil: IR (CH_2Cl_2, cm^{-1}) 1710, 1648; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.18 (dd, *J* = 11.0 Hz, *J* = 17 Hz, 1H), 6.00 (d, *J* = 17.0 Hz, 1H), 5.89 (s, 1H), 5.38 (d, *J* = 11.0 Hz, 1H), 2.50 - 2.35 (m, 4H), 1.11 (t, *J* = 7.5 Hz, 3H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.9, 154.8, 154.3, 128.1, 125.8, 119.0, 107.4, 25.4, 19.9, 13.4, 13.2. HRMS (EI) Calcd. for $C_{11}H_{14}O_2$: 178.0994. Found: 178.0990.

3,4-Di-*n*-butyl-6-(1-ethoxyvinyl)-2-pyrone, 4r. A dioxane solution (12 mL) of 4-chloro-2,3-di-*n*-butyl-2-cyclobutenone (0.392 g, 1.83 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (69 mg, 5 mol%) was treated with 1-ethoxyvinyltri-*n*-butyltin (0.775 g, 2.01 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and then at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.50) gave 0.305 g (60%) of **4r** as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1706, 1648; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.23 (s, 1H), 5.05 (d, *J* = 2.7 Hz, 1H), 4.34 (d, *J* = 2.7 Hz, 1H), 3.82 (q, *J* = 6.9 Hz, 2H), 2.44 - 2.34 (m, 4H), 1.46 - 1.21(m, 11H), 0.91 - 0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.7, 153.4, 151.7, 125.1, 103.8, 86.6, 63.5, 32.3, 31.1, 30.8, 26.4, 22.7, 22.6, 14.3, 13.8, 13.7. HRMS (EI) Calcd. for $C_{17}H_{26}O_3$: 278.1882. Found: 278.1881.

3,4-Diethyl-6-(1-propenyl)-2-pyrone, 4s. A dioxane solution (12 mL) of 4-chloro-2,3-diethyl-2-cyclobutenone (0.286 g, 1.8 mmol, 1.0 equiv) and $PhCH_2PdCl(PPh_3)_2$ (68 mg, 5 mol%) was treated with 1-propenyltri-*n*-butylstannane (1 : 2 *E* : *Z* by NMR, 0.656 g, 1.98 mmol, 1.1 equiv) in 2 mL of dioxane at 45 psig of CO at 50 °C for 12 h and then at 100 °C for 8 h. Work up and purification by flash silica gel chromatography (1 : 4 EtOAc / hexanes, R_f = 0.47) gave 0.225 g (65%) of **4s** (1 : 1 ratio of E : Z) as a yellow oil: IR (CH_2Cl_2, cm^{-1}) 1706, 1659, 1619; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.57 - 6.49 (m, 1H), 5.91 - 5.76 (m, 5H), 2.48 - 2.33 (m, 8H), 2.07 (d, *J* = 6.0 Hz, 3H), 1.82 (d, *J* = 6.9 Hz, 3H), 1.13 - 1.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ

163.1, 163.0, 156.7, 155.4, 154.7, 154.5, 133.4, 132.2, 124.3, 124.1, 122.9, 121.3, 108.9, 105.4, 25.45, 25.41, 19.8, 18.2, 15.6, 13.4, 13.5, 13.2, 13.2. HRMS (EI) Calcd. for $C_{12}H_{16}O_2$: 192.1150. Found: 192.1142.

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